Objectives:- 1) To classify receptor & it's action.
2) To mention drug's response on ~~action~~ function receptor.

eg:- when there's a patient having any deasease, he will take drugs; these drugs will be absorpeed and distributed to all parts of the body in equillibrium but each specific drug will act on specific sites in body these sites are known as cellular site of drug action. eg:- CNS → Neurons.
GIT → Epithelial cells
Kidney → Nephrons.
Liver → hepatocytes.

these drugs will attach to the cell membranes of these cells. & will interact with either ion channel, enzymes or receptors, more than 90% of drugs interact with receptors. (Receptors can be on cell memb. or intracellular) or outside the cell.

After entering the cell → lipid soluble.
→ or aqueous but can enter through pores in hepatocytes.
→ or by transporters absorped through nephrons.

inside the cells can interact either with Carrier proteins, enzymes or DNA.
↓
increase or decrease it's action.

eg. * Int. of drug within the cell:-
Ampicillin & propenecid both are acidic drugs competetively interact with each other for binding to the acidic receptors in tubular cells of Nephrons to be excreated, Propenecid has higher afinity so it's excreated increasing the concentration of Ampicillin in blood thus increasing ~~the~~ it's therapeutic effect. (acidic drugs compete for acidic receptor).

* Outside the cell:- non receptor / without enzymes or carriers.

* ((Chemical)):- 1) patient with gastritis HCl ↑
treatment → antiacids $Al(OH)_3$, milk.

$HCl + Al(OH)_3 \rightarrow AlCl_3 + H_2O$
salt

Releive from gastritis. ← Ph ↑

2) Over dose of heparin → ((bleeding)).
treatment → protamin + Heparin → complex
(basic) (acidic)
decreases action of Heparin thus stop bleeding.

3) Iron poisioning → drug (desferrioxamine) makes chelations → Iron ↓.

∴ To increase excreation of poisons we have to change the ph of Urine against the ph of that drug in order to ionize it in the Urine & thus excreated

eg:- Basic drug poisoning → give acidic drug → poison ionizes in the Urine → excreated.

4) Milk + Iron or tetracycline →

tet ← Ca^{++} → tet

not absorped ← (Complex) ←

Conc:- Treatment of certain disorders or Overdosage, poisoning or side effects by certain drugs based on chemecial Interaction of drug.

(*) (physical)) :- (1) Charcoal :- is a substance that adsorbs the particals on its surface used in treatment of poisons which aren't still absorbed by GIT & the poison is excreated.

(2) Mannitol :- has Osmotic / diuretic effect.
Used in case of poisoning and raised intracranial pressure.
↓
increases the concen. of solute in B.V thus attracts H_2O, vasodilation in nephrons → excreation ↑.

* Main principles of drug Action:-

1) Modification :- eg. hypertension :- we give antihypertensive.
2- Renal Insufficiency :- diuretics. (feurasimide)
3- fever :- Antipyretics.
to modify the action of what's already present.

2) Replacement :-
3) Cytotoxic :- antiviral, antibacterial.

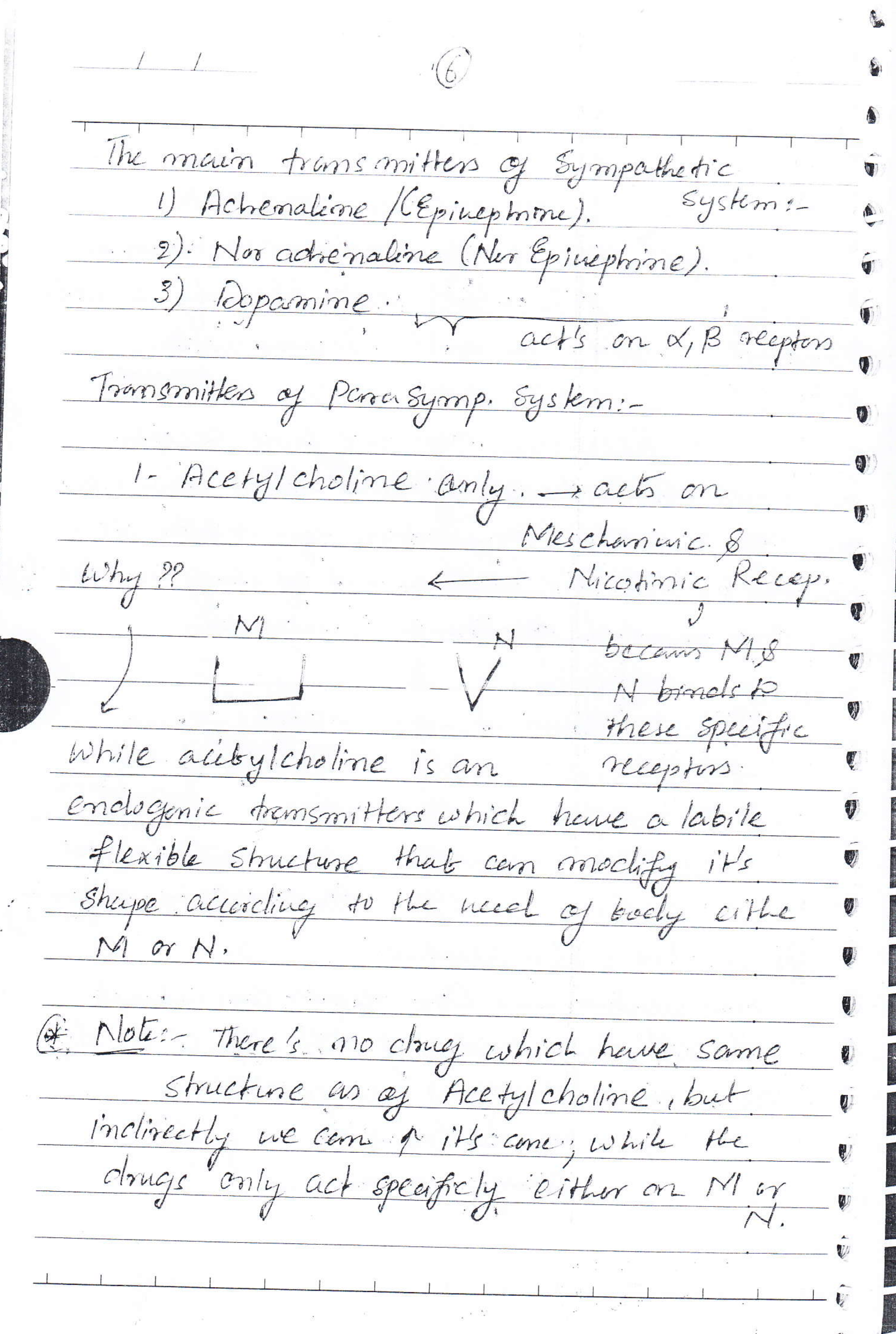
4) When there is need to subst :-
diebetics → Insulin.
Anaemia → Iron.

* Does the drug introduce new action on body? No it only modifies, replaces or Kills what's ~~only~~ already found.
but if have new action means problem occurs.

* Silent Receptors: there are some receptors found outside the cell which binds to drugs but doesn't produce any action eg. → albumin.
act as reservoir when amount of drug in blood↓ drug bounded to albumin is released.

drug + albumin↓ → concent. of free drug ↑ → we have to decrease the dose
((in case of hypoalbuminemia)).

* Selective & Non selective:
Non-selective → One receptor can interact with diff. drugs producing diff. effects on diff. cells. eg. → (Phenergan) given for children.
on muscle → contract
Kidney, neurons...



The main transmitters of Sympathetic System:-

1) Adrenaline (Epinephrine).
2) Nor adrenaline (Nor Epinephrine).
3) Dopamine.

act's on α, β receptors

Transmitters of Para Symp. System:-

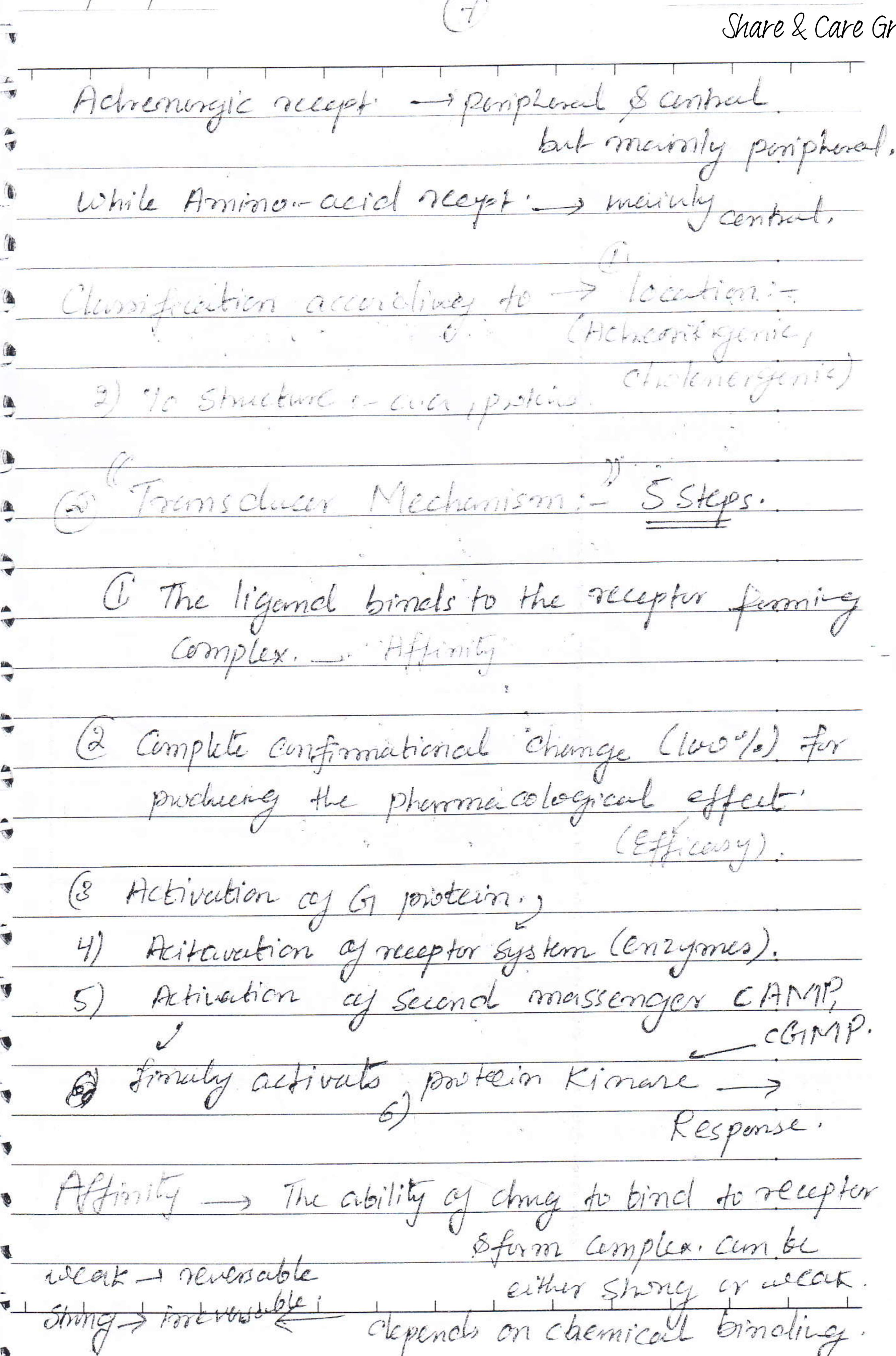
1- Acetylcholine only. → acts on Meschariuic & Nicotinic Recep.

Why ?? ←

because M & N binds to these specific receptors.

While acetylcholine is an endogenic transmitters which have a labile flexible structure that can modify it's shape according to the need of body eithe M or N.

* Note:- There's no drug which have same structure as of Acetylcholine, but indirectly we can ↑ it's conc; while the drugs only act specificly either on M or N.



Adrenergic recept → peripheral & central
but mainly peripheral.

While Amino-acid recept → mainly central.

Classification according to → ① location :- (Adrenergic, Cholinergic)

2) To Structure :- a.a, protein

② "Transducer Mechanism :-" 5 Steps.

① The ligand binds to the receptor forming complex. — Affinity

② Complete conformational change (100%) for producing the pharmacological effect (Efficacy).

③ Activation of G protein,

4) Activation of receptor system (enzymes).

5) Activation of second messenger cAMP, cGMP.

6) finally activate protein Kinase → Response.

Affinity → The ability of drug to bind to receptor & form complex. can be either strong or weak. depends on chemical binding.

weak → reversable
strong → irreversable

Efficacy → The ability of drug to form complex & to ~~chang~~ induce conformational change 100%.

Adrenaline → Cardiac muscle.
(B_1). → G.P.(GS) → Adenylate
(Same family).
Acetylcholine
(M).

Adrenaline (tachycardia).
↓ (B_1)
Cardiac muscle
↓
G.Protein (GS). — Transducer mechanism
↓
Adenylate cyclase
↓
cAMP
↓
Protein Kinase (A)
↓
Ca^{++} channels open.
myosin ←
actin → Contractility ↑.

Acetylcholine
↓ (M)$_1$
Cardiac muscle
↓
(G I)
↓ inhibits
(M) Adenylate cyclase.

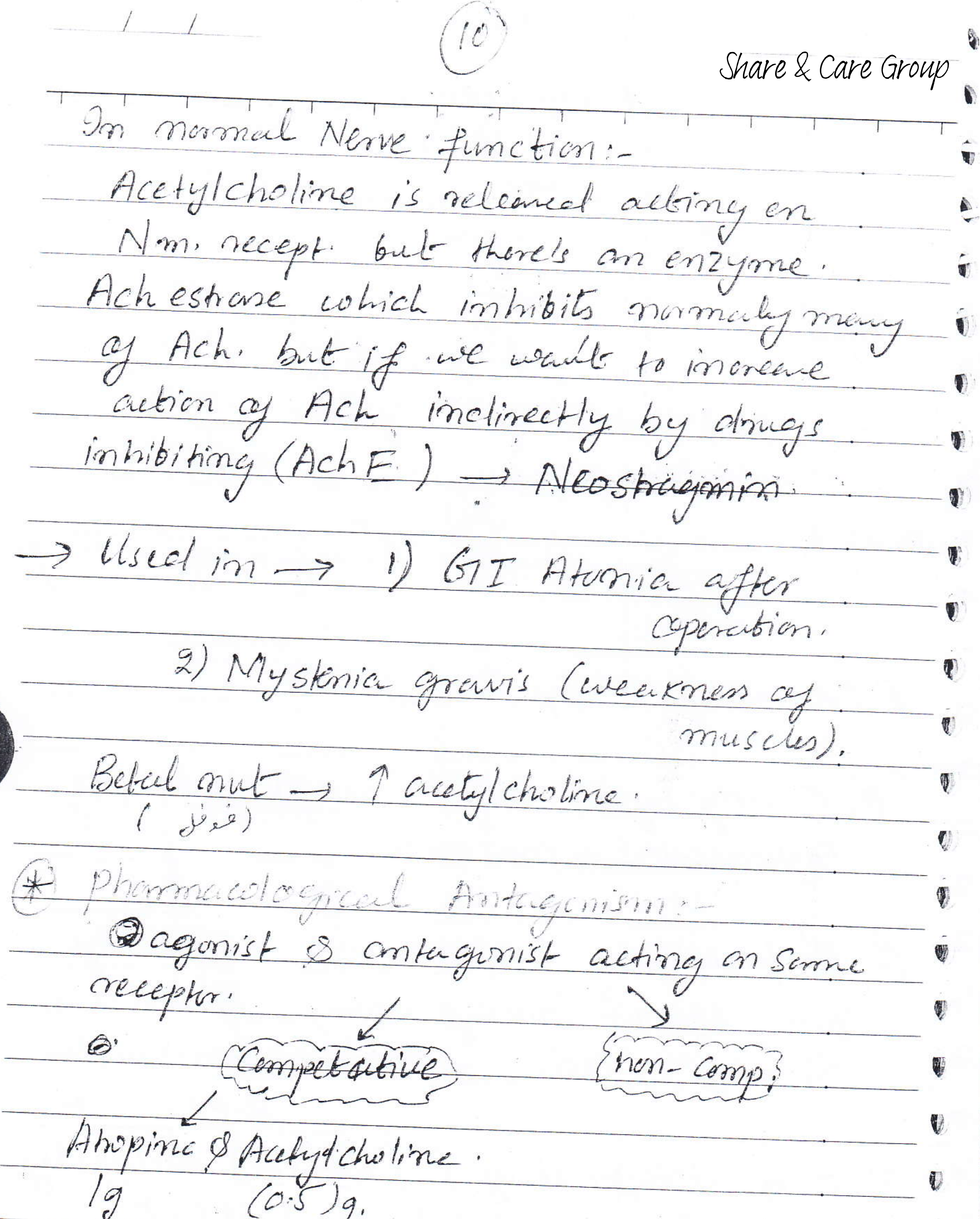
∴ Acetylcholine & Adrenalin on cardiac muscle → (β_1) physiological Antagonism.

* Decreasing BP by 2 mecha :-

① directly by blocking α_1 receptor by giving Antagosit → prozonid.

(2 Indirectly by activating α_2 receptors by giving agonist (methyl dopa) → decrease discharge of Nadr → ~~decrease~~ vasodilation, B.P↓.

3) or by Antagonist of β_1 (blocker) indirectly reducing B.P by ↓ C.output, ↓ H.Rate & ↓ Renin release (Blocking ~~Ang~~ Angiotensin II).
& ↓ peripheral resistence.
also used in arrythemias.
eg :- propanolol.
Athenalol.



In normal Nerve function:-

Acetylcholine is released acting on N m. recept. but there's an enzyme. Ach estrase which inhibits normaly many of Ach. but if we wants to increase action of Ach indirectly by drugs inhibiting (AchE) → Neostigmin

→ Used in → 1) GIT Atonia after operation.

2) Myskenia gravis (weakness of muscles).

Betel nut → ↑ acetylcholine.
(فوفل)

(*) Pharmacological Antagonism:-

② agonist & antagonist acting on same receptor.

① Competitive | non-Comp.

Atropine & Acetylcholine.
1g (0.5)g.

Atropine is antagonist
will displace Acetyl. but
if we increase conc. of
Acetyl from 0.5 to 1.
it can produce it's max. effect

∴ In Comp. pharm. antagonism:-
the agonist can produce it's max. effect if it's found in high concent. in the presence of antagonist.

Non- Comp:- { Active site
Another site

Antagonist binds to another site & produces conformational changes on receptor preventing the binding of Agonist on active site → (−) non-comp.
or if vise versa → (+) non- Antagonism.

In this case no maximum effect is produced.

(*) Upregulation ⇒ ↑ no. of receptors by continous use of antagonists eg:- propanolol.
sudden stop → malignant hypetension.
because lot of receptors so small amount of adrenaline ↑ B.P. → gradualy decreasing the dose.

(*) Downregulation ⇒ ↓ no. of receptors by continous use of agonists. eg:- salbutamol.
by prolonged use / no effect.

~~Desensitization.~~

→ No of recept are same but confirmational changes so that no effect.

What's the imp. of Transducer mechanism?

→ To know the action of the drug in the body, some drugs bind to the receptor & have long term effect for 20 hours...
& some of them have short effect, so we have to take it more than once..

— x — x — x —

"Autonomic Nervous System"

1) The main Transmitter & it's action.
2) The Adrenergic transmitter
3) The drugs acting on adrenergic system.

A.NS → involuntary functions in body.

dopamine ⇒ main action in CNS.
in peripheral → on mysentric B.V.
→ on Renal B.V.

D_1 ↓ Periphery (Vasodilation) to increase renal perfusion in cardiogenic shock.

D_2 → CNS → Adenohypophysis :- Regulate the prolactine release.
(promocreptine) → Agonist
↓ Stop the high release 1.25mg of prolactine.

{Negrostretial zone} (limbic system) ⇒ dopamine regulate movment

parkinsonism :- no regular of mov. due to degeneration of dopamin neurons.
(L-dopa) ← (treatment)
(lipodopa) agonist act on D_2 receptors.
here we can use promocreptine but it requires high doses & when we increase dose → many side effects appear.
So here drug of choice L-dopa
but some times we can combine if there is no effect of L-dopa.

* Chemo-receptor-trigger zone :- dopamine act on D_2 zone & induce vomiting. (Emesis).

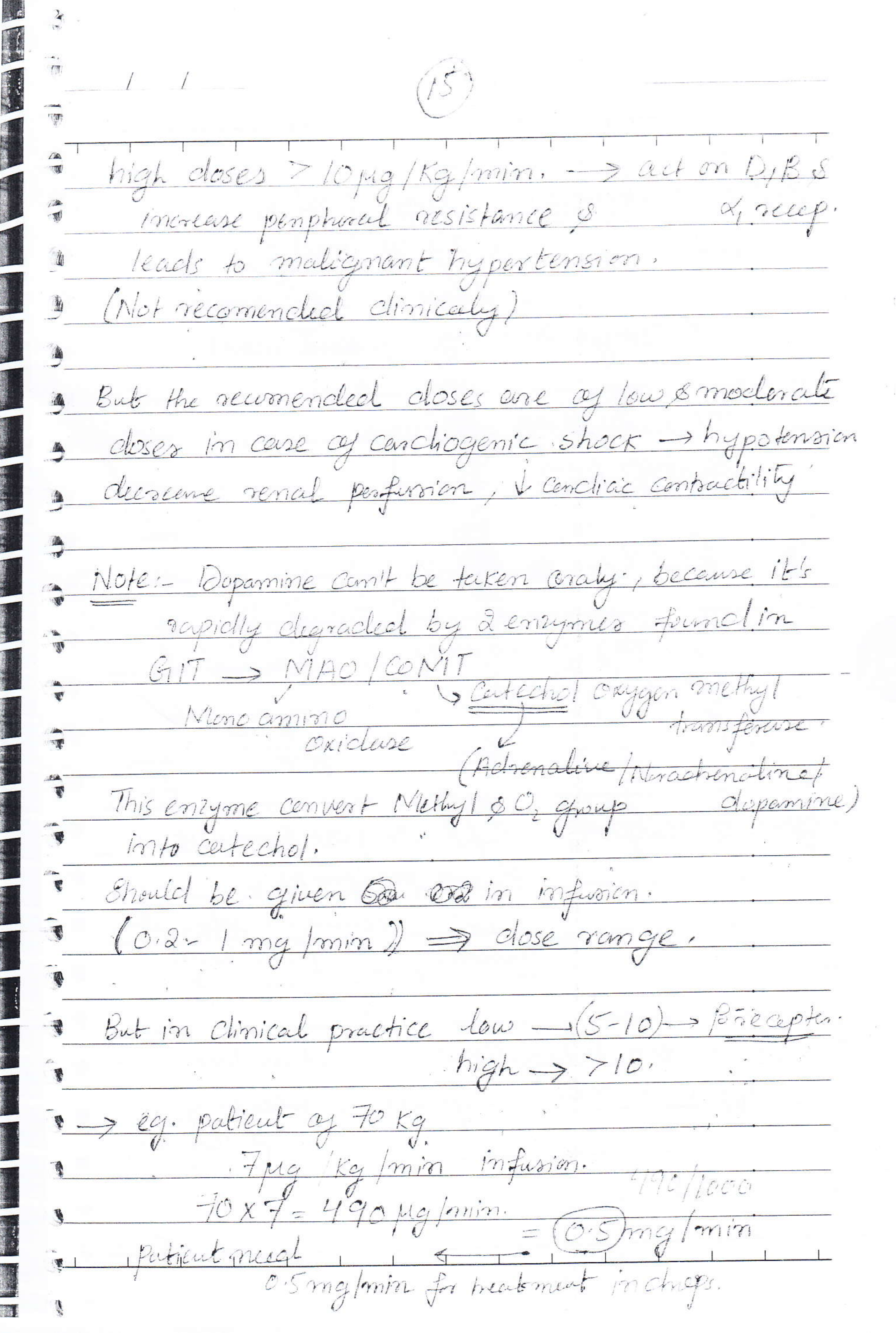
Treatment ⇒ Antagonist → Chlorpromazine
Antiemesis, but it has side effects :-
1) parkinsonism in some patient
2) hyperprolactenemia in women.
because it blocks all the areas of D_2.

Side effect of bromocreptine ⇒ Emesis.
(& L-dopa)

dopamine also act on α, β in addition to D.
dopamine effect usualy depend on dose.
at low dose < 5 μg/Kg/min acts on peripheral system on D_1 & produce vasodilation. (good in shock eg. cardiogenic shock → ↓ renal perfusion situations).

* Note :- There are many drugs used for treatment of Emesis because the mechanism of emesis include different types.

moderate dose of 5-10 μg/Kg/min → act on D & B_1 receptors



high doses > 10 μg / Kg / min. ⟶ act on D, β & α_1 recep.
increase peripheral resistance &
leads to malignant hypertension.
(Not recomended clinicaly)

But the recomended doses are of low & moderate doses in case of cardiogenic shock → hypotension
decreme renal perfusion, ↓ cardiac contractility

Note:- Dopamine can't be taken oraly, because it's rapidly degraded by 2 enzymes found in
GIT → MAO / COMT
Mono amino oxidase
↳ Catechol oxygen methyl transferase
(Adrenaline / Noradrenaline / dopamine)

This enzyme convert Methyl & O_2 group into catechol.

Should be given ~~as~~ ~~IV~~ in infusion.
(0.2 - 1 mg / min) ⟹ dose range.

But in clinical practice low ⟶ (5-10) → β receptor.
high → > 10.

→ eg. patient of 70 Kg
7 μg / Kg / min infusion.
70 x 7 = 490 μg / min.
490 / 1000
= (0.5) mg / min
patient need ←
0.5 mg / min for treatment in drops.

250mg/500ml dextrose. 1mg/2ml.
("0.5mg/1ml" of dextrose.
dopamin fixed, but
we change according to patient need.

1ml = 20 drops = 0.5mg.
20 drops/min.

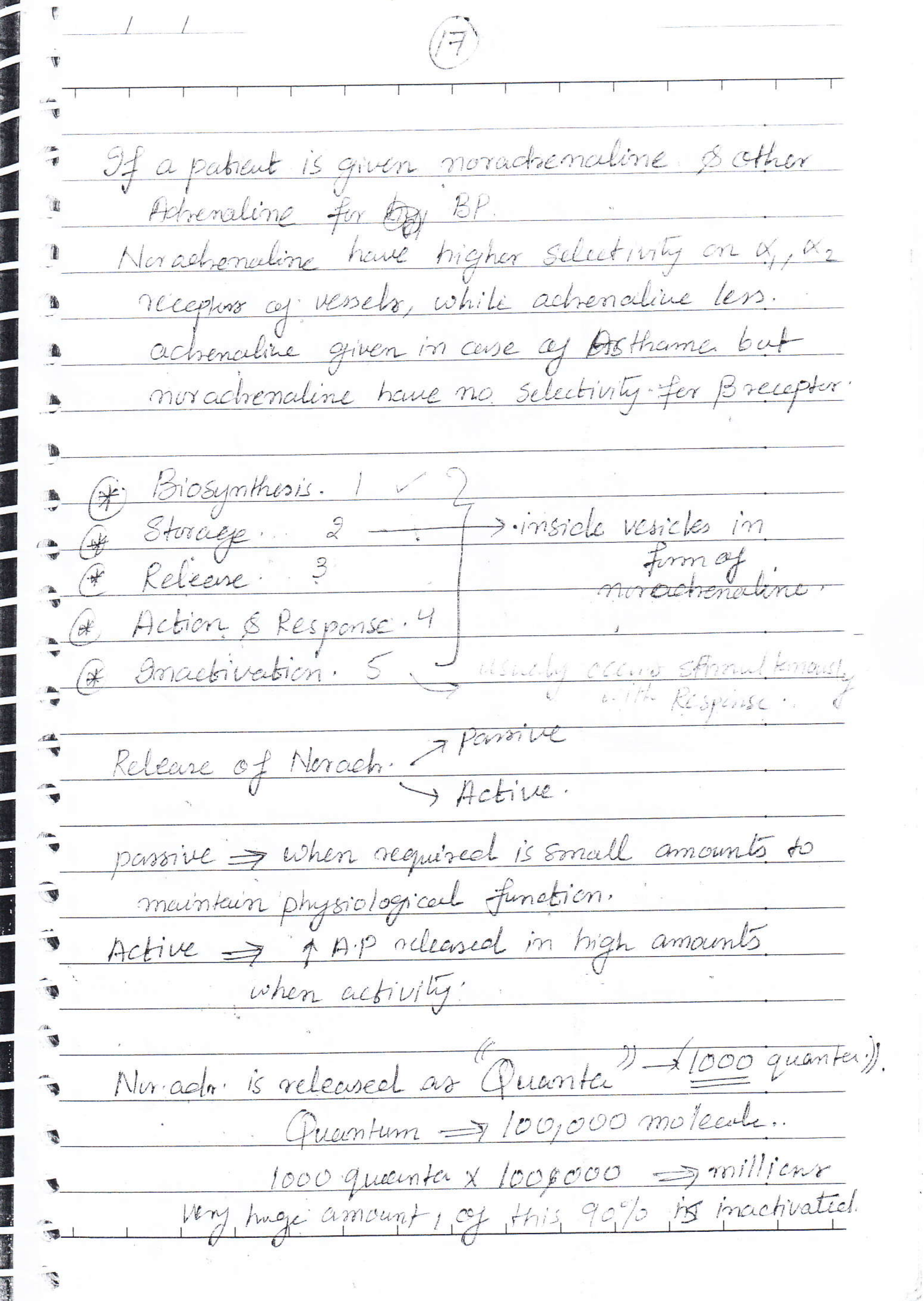
eg:- 50 × 7 = 350 μg/kg/min. 350/1000
0.35mg ≃ 0.4mg

0.5mg = 20 drops.
0.4mg = x

$$x = \frac{0.4 \times 20}{0.5} = 16 \text{ drops}$$

2 types of receptors :- α/β ⇒ post synaptic
α_2 ⇒ presynaptic
(decrease noradrenaline discharge).
on neurons terminal.

(+) diff. between Adrenaline & noradrenaline.
differs in activity depends on selectivity of receptors.



If a patient is given noradrenaline & other Adrenaline for BP.
Noradrenaline have higher selectivity on α_1, α_2 receptors of vessels, while adrenaline less.
adrenaline given in case of Asthama but noradrenaline have no selectivity for β receptor.

- (*) Biosynthesis. 1 ✓
- (*) Storage. 2 → inside vesicles in form of noradrenaline.
- (*) Release. 3
- (*) Action & Response. 4
- (*) Inactivation. 5 → usually occurs simultaneously with Response.

Release of Noradr. → Passive / → Active.

passive ⇒ when required is small amounts to maintain physiological function.
Active ⇒ ↑ A.P released in high amounts when activity.

Nor.adr. is released as "Quanta" → (1000 quanta).
Quantum ⇒ 100,000 molecule..
1000 quanta x 100,000 ⇒ millions
very huge amount, of this 90% is inactivated.



Only 10% reachs the receptors to produce action. enzymes inactivate 90%.

Action ⇒ presynaptic ⇒ (α_2) feedback inhibition of ~~dopa~~ noradr. release.

post synaptic ⇒ α_1, β_1, β_2.

To stop release we give agonist (methyldopa or cholidin)).

we can benefit by this in treating hypertension.

(*) Inactivation :- 3 ways.

1) Reuptake → 1, 2

means returns

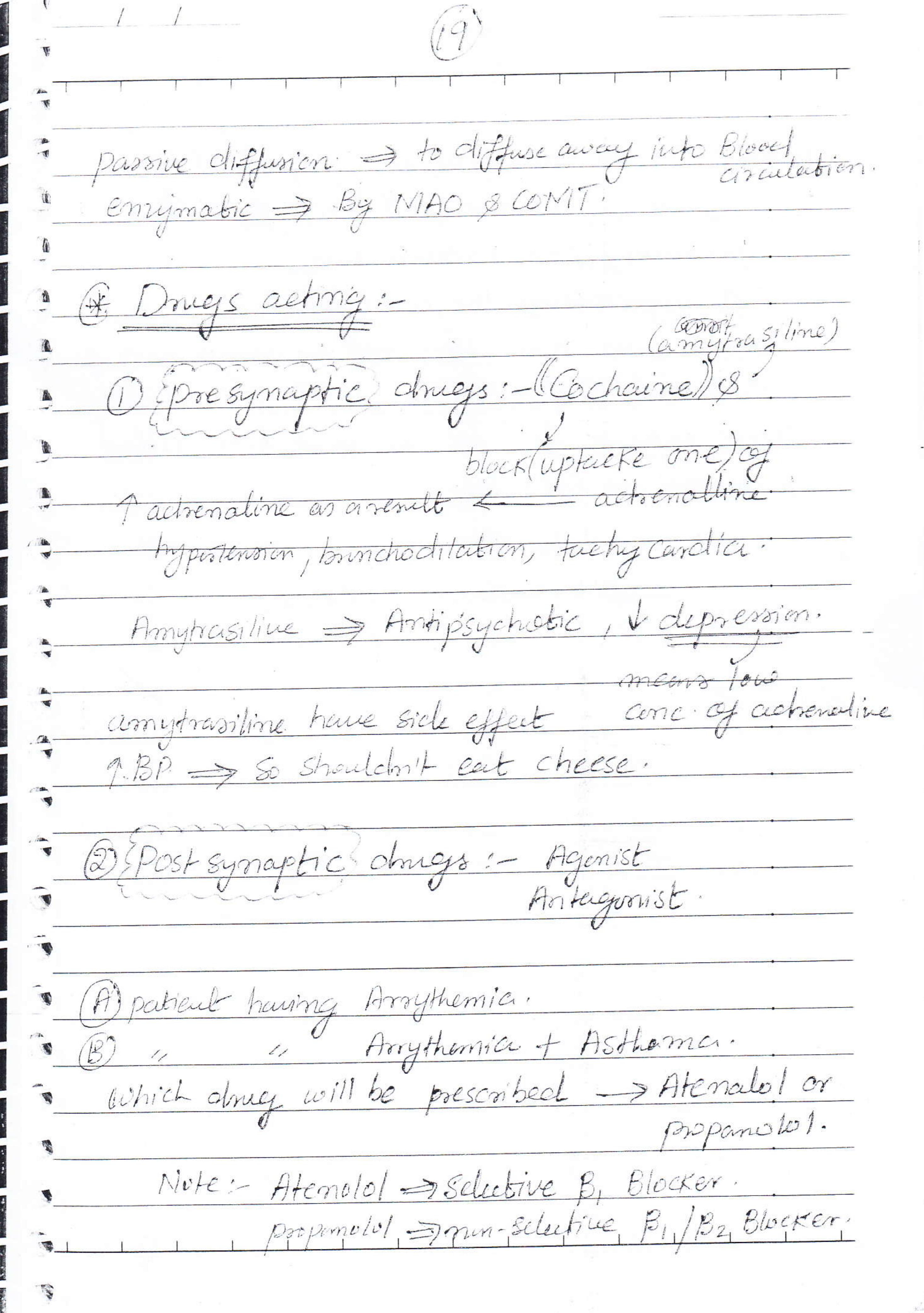
1) back to neuron ~~after release~~ by carrier. inside neuron either inactivated by MAO or stored.

2) ~~uptake to other neuron~~ or tissue, which is there degraded by another enzyme!

by COMT

2) Passive diffusion.

3) Enzymatic destruction.



passive diffusion ⇒ to diffuse away into Blood circulation.
enzymatic ⇒ By MAO & COMT.

⊛ Drugs acting :-

① {presynaptic} drugs :- ((Cochaine)) & (amytrasiline)

(Cochaine) ↓ block (uptacke one) of adrenalline ⟶ ↑ adrenaline as a result

hypotension, bronchodilation, techycardia.

Amytrasiline ⇒ Antipsychotic, ↓ depression.
(depression means low conc. of adrenaline)

amytrasiline have side effect
↑ BP ⇒ So shouldn't eat cheese.

② {Post synaptic} drugs :- Agonist
Antagonist.

Ⓐ patient having Arrythemia.
Ⓑ " " Arrythemia + Asthama.
Which drug will be prescribed ⟶ Atenalol or propanolol.

Note :- Atenolol ⇒ Selective β_1 Blocker.
propanolol ⇒ non-selective β_1 / β_2 Blocker.



patient (B) we can't give him propanalolol.
because non-selective will block β_1 & (β_2)
producing Bronchoconstriction
& aggrevating the condition.
So we give him Atenolol for arrythymia +
Salbutamol for Asthma.
While patient (A) we can give him either
propanolol or Atenolol.

— x — x — x — x —

(ANS (2) Cholinergic System)

(1) The main transmitter + site of action.
(2) Cholinergic transmission.
(3) drugs acting & clinical use.

Muscarinic & Nicotinic receptors.
main trans. → Acetylcholine.

Site of Action of Acetylcholine :-
1) Ganglia (first site of action) Nicotinic N_g
bind to → ganglionic receptor.

→ Acetylcholine (1) stimulate ganglia in both sympathetic & parasympathetic NS, in parasym. ↑ release of acetylcholine, while in sympathetic increase release of Adrenaline & noradrenaline. produces lots of disturbances, there is no drug that does the action of acetylcholine but instead Ganglia blockers ⇒ ((Trimethaphan)) ⇒ severe hypotension because decreases both symp & parasymp. used only in case of emergencies in malignant hypertension. (No clinical Use)) tachycardia, hypotension.

(2) Post ganglionic - parasympathetic neurons innervatis effectors organs.

(3) Post ganglionic Sympathetic neurons innervatis Sweat glands (Exception all Symp. secreatis nor adrenaline except here in sweat gland Acetylcholine)).

(4) Motor neuron (Somatic NS) release acetyl choline on striated muscles on NM receptor (nicotinic muscular) contraction.

(*) Nicotinic Recep. → NM
→ NG (ganglionic).

Drugs blocking the 4th site of action decrease muscular activity (muscle relaxant).
(D- Tubocurarine. & Gallamin)).

used in Pre Operations to reduce use of anesthesia & to relax musles.

(5) CNS ⇒ good for memory.
Alzahymer deasese ⇒ ↑ acetylcholine release.

((5 steps of Synthesis)).

Inactivation by enzyme acetylcholine estraze.

Acetyl Choline
↓ Acetyl Ch estrase ⊖

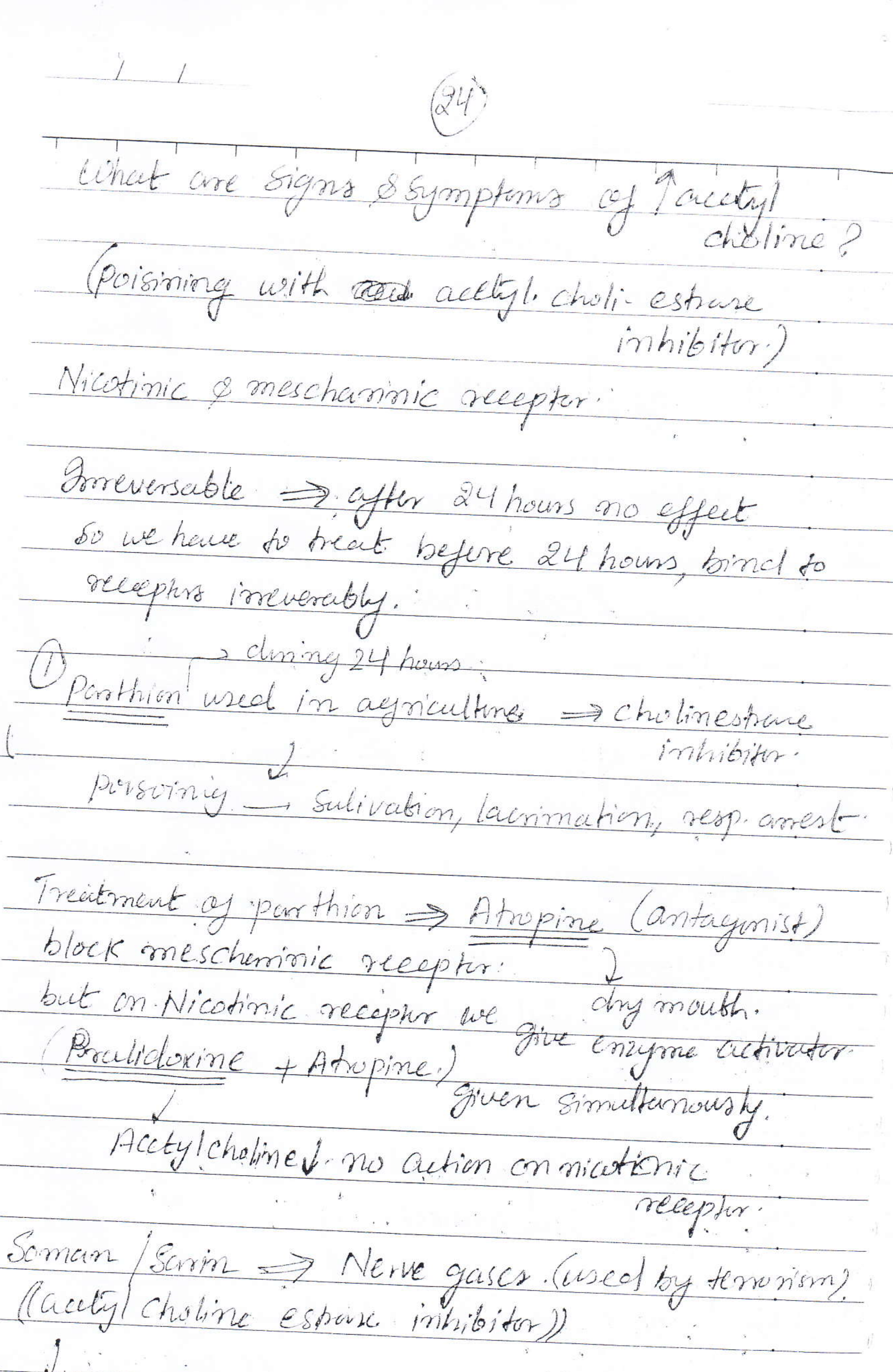
Acetyl → Kreb's cycle

Choline returned back to neuron for resynthesis of Acetyl choline.

True enzyme :- Which only degrades the endogenous Acetyl chol. not that which mimic like drugs.

False enzyme :- degrades drugs resembling acetylcholine ((local anaesthetics)).

((Acetyl choline enzyme Inhibitor)) → ↑ concen. of Acetylcholine.
(Estrase)
indirectly increase Acetyl-choline by blocking the enzyme not directly by receptors.



What are signs & symptoms of ↑ acetyl choline?

(poisining with ~~acd~~ acetyl. choli- estrase inhibitor.)

Nicotinic & meschaminic receptor.

Irreversable ⇒ after 24 hours no effect so we have to treat before 24 hours, bind to receptors irreverably.

① Parthion used in agriculture ⇒ cholinestrase inhibitor.
→ during 24 hours.

↓

poisoning → Salivation, lacrimation, resp. arrest.

Treatment of parthion ⇒ **Atropine** (antagonist) block meschaminic receptor.
↓ dry mouth.

but on Nicotinic receptor we give enzyme activator.

(**Pralidoxine** + Atropine) given simultanously.

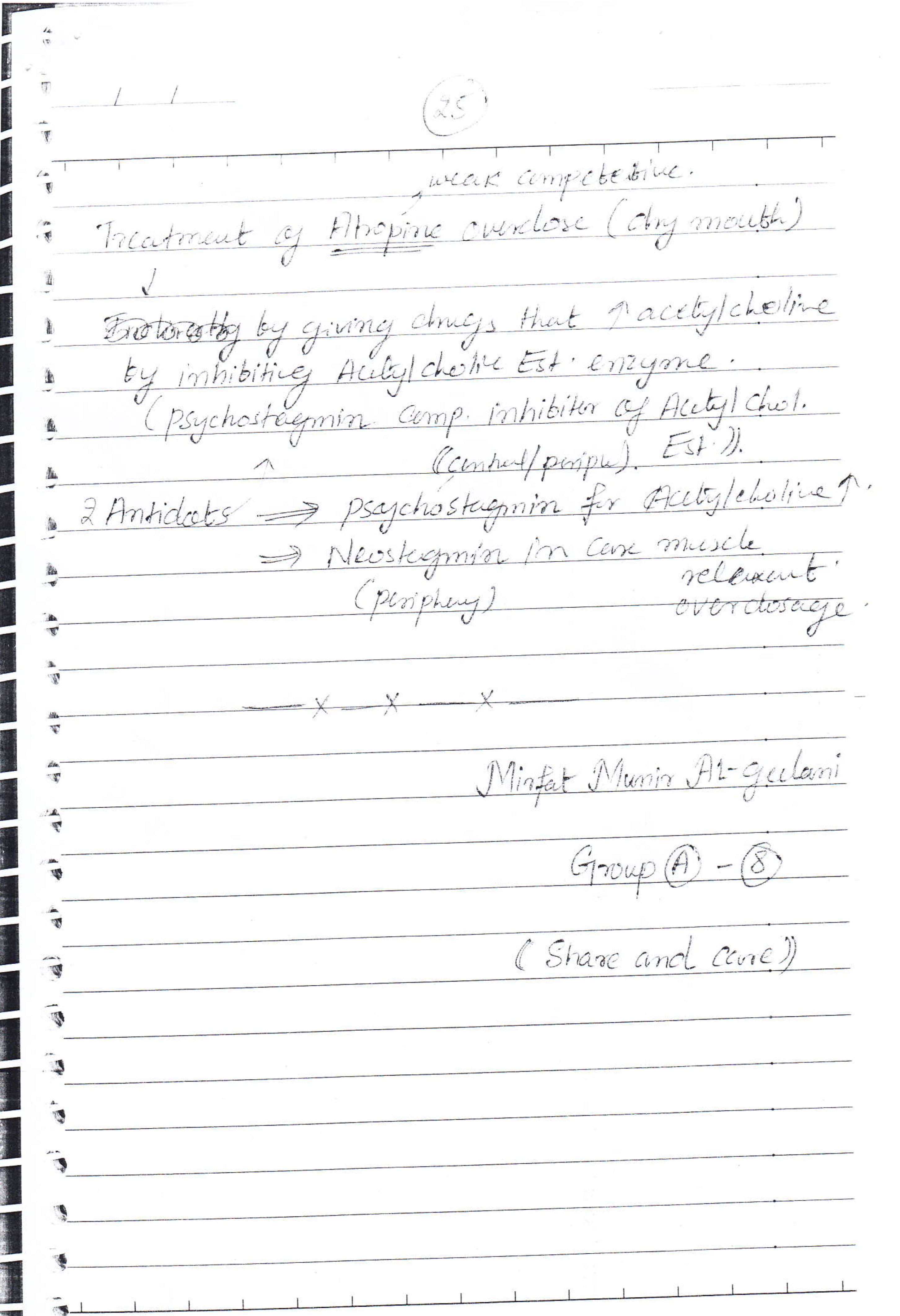
↓

Acetylcholine ↓ no action on nicotinic receptor.

Soman / Sarin ⇒ Nerve gases. (used by terrorism)
((acetyl choline estrase inhibitor))

↓

Treatment of poising by pralidoxine + Atropine.



Treatment of Atropine (weak competitive.) overdose (dry mouth)

↓

~~[illegible]~~ by giving drugs that ↑ acetylcholine by inhibiting Acetylcholine Est. enzyme.
(psychostagmin comp. inhibitor of Acetyl Chol. Est.)).
↑ ((central/periph).

2 Antidots ⇒ psaychostagmin for Acetylcholine ↑.
⇒ Neostagmin in case muscle relaxant overdosage.
(periphery)

— x — x — x —

Minfat Munir Al-geelani

Group (A) - (8)

(Share and care))